

Assessment of irisin levels in patients with bipolar depression and unipolar depression

Irisin levels in patients with unipolar and bipolar depression

Gamze Erzin¹, Rabia Nazik Yüksel², Miraç Barış Usta³, Canan Topçuoğlu⁴, Sibel Örsel¹¹ Department of Psychiatry, Dışkapı Yıldırım Beyazıt Training and Research Hospital² Department of Psychiatry, Ankara City Hospital³ Department of Child and Adolescent Psychiatry, Ondokuz Mayıs University⁴ Department of Biochemistry, Ankara City Hospital, Ankara, Turkey

Abstract

Aim: Irisin is a myokine and adipokine which has neural effects such as playing a role in neural proliferation. There are studies in the literature reporting that irisin could be associated with neurodegenerative processes. Therefore, in this study, we aimed to evaluate the irisin levels in patients with bipolar depression and major depressive disorder.

Materials and Methods: Thirty patients with bipolar disorder (BD) depressive episodes, 28 patients with major depressive disorder (MDD) and 30 healthy controls (HCs) were included in the study. Sociodemographic and clinical data were collected from each participant. Serum irisin levels were determined by enzyme-linked immunosorbent assay (ELISA) kits, and the severity of the depression was measured by the Hamilton Depression Rating Scale.

Results: There was no statistically significant difference between patients with MDD, bipolar disorder depressive episodes and healthy controls in terms of irisin levels. The statistical analysis revealed significant negative correlations between levels of irisin and duration of illness ($r=-0.500$, $p<0.01$) in MDD. Irisin serum level was found to be negatively correlated with the number of depressive episodes ($r=-0.620$, $p<0.01$) in patients with MDD.

Discussion: Irisin's role in the development of depression in patients with coronary artery diseases and patients having strokes has been studied previously in the literature. Our study is the first that evaluated levels of irisin in patients with bipolar depression and major depressive disorder. No statistically significant difference was obtained in these three groups in terms of irisin levels. Further studies may help to understand the role of irisin in the underlying mechanism of depression.

Keywords

Irisin; Depression; Bipolar disorder; Myokine; Duration of illness

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Corresponding Author: Gamze Erzin, Dışkapı Yıldırım Beyazıt Training and Research Hospital Psychiatry Department, Altındağ, Ankara, Turkey.

E-mail: gamze.erzin@gmail.com P: +90 312 596 2000

Corresponding Author ORCID ID: <https://orcid.org/0000-0001-8002-5053>

Introduction

Bipolar disorder has an estimated prevalence of about 1.2% and significant morbidity rates including the risk of premature death by suicide [1]. Patients with bipolar disorder who are in their depressive phases are mostly misdiagnosed with unipolar depression [2]. Treatment of these patients for unipolar depression may also increase the risk of manic state [3]. Previous studies have suggested that almost 40% of patients with bipolar disorder were misdiagnosed with unipolar depression or psychosis [4, 5]. On the other hand, underdiagnosis remains a significant problem, which causes undertreatment and may worsen the outcome of bipolar disorder [5]. According to our knowledge, however, myokines have not been examined as potential biomarkers for BD.

Irisin is known as a myokine and acts on subcutaneous adipose tissue, increasing thermogenesis, and energy consumption [6]. Irisin is increased by activation of proliferator-activated receptor (PPAR) coactivator, which is released as an anti-inflammation marker in the cardiovascular and nervous system [7]. The therapeutic potential of irisin in diabetes and obesity aroused great interest [8], and also PPAR γ activation was found to be lower in patients with schizophrenia [9], which likely share a genetic origin [10]. Preclinical and clinical evidence has shown that irisin could induce brain-derived neurotrophic factor (BDNF) expression in the ventral tegmental area and the hippocampus [11]. Therefore, irisin levels may be associated with this pathway and serve as potential biomarkers for BD and MDD.

This study aimed to examine the role of irisin levels in BD. In this context, irisin levels were compared between BD, MDD, patients and healthy controls. We hypothesized that irisin levels would be lower in patients with BD and MDD compared to healthy controls (HCs).

Material and Methods

This study was designed to include patients with BD or patients with MDD diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) who presented to our hospital and were compliant with the inclusion criteria (aged between 18-65 years). This study was approved by the ethics committee of Ankara Numune Training and Research Hospital (date: 17.01.2018; number: E-17-1628). The HC group did not have any psychiatric and neurologic disease history.

Laboratory tests results, including complete lipid parameters, fasting blood glucose (FBG) and insulin measurements were recorded on blood samples from each participant. Patients with bipolar disorder depressive episodes, and MDD were evaluated using the Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale. HAM-D was adapted for validity and reliability in Turkish by Akdemir et al [12, 13]. Young Mania Rating Scale was adapted for validity and reliability in Turkish by Karadağ et al. [14, 15].

Sociodemographic data form included age, gender, duration of illness, number of depressive and manic episodes, number of hospitalization, age of onset of mental illness of patients.

Exclusion criteria were additional psychiatric and neurological disorders (such as mental retardation, alcohol or substance

abuse) obesity, known inflammatory disease or use of immunosuppressive agents, pregnancy, cardiovascular disease, malignancy.

Blood sampling

After a 12-hour night fast, 5 milliliters (mL) of fasting blood samples were collected from each participant. Blood samples were separated from sera within 30 to 60 minutes of collection and stored at -80°C until required for analysis. On the same day, Hamilton Depression Rating Scale and the Young Mania Rating Scale were measured for each participant.

Irisin analysis

Levels of serum irisin were determined using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, Elabscience Biotechnology Co. Ltd. WuHan, P.R.C., Catalog No: E-EL-H2254, LOT: AK0017NOV25085) for quantitative determination in humans. The measuring range was 0,16-10 ng/mL. The sensitivity was 0,10 ng/mL and CV% values were <10%.

Statistical analysis

Statistical analysis was performed on SPSS version 21.0 software (SPSS, Chicago, IL). The conformity of the variables to the normal distribution was evaluated visually (histogram and possibility graphs) and with analytical methods (Kolmogorov-Smirnov/Shapiro-Wilks tests). The Chi-square test, Fisher's Exact test, and Student's t-test were used for values conforming to the normal distribution and the Mann-Whitney U-test for those with non-normal distribution. The relationship between biochemical variables was evaluated with the paired t-test and the Spearman Correlation test and for three groups, One-Way ANOVA was used. For post-hoc analysis, Tukey test was used. The level of statistical significance was determined as p<0.05.

Results

In this study, we have recruited 30 patients with bipolar disorder, 28 patients with MDD, and 30 HCs. There were no differences between the three groups (BD, MDD, and HCs) in terms of age and gender and there were not any differences between BD and MDD in terms of HAM-D scores (Table 1).

Table 1. Comparison of sociodemographic and clinical data between Bipolar Disorder Depressive Episode, MDD, and HC groups

Study Parameter	Bipolar disorder group (n: 30)	MDD group (n: 28)	HC group (n: 30)	Test statistics	P
Age	35.4 ± 8.5	40.4 ± 13.4	38.0 ± 9.4	F:1.633	0.201
Gender	Female	%60.0 (n:18)	%71.4 (n:20)	x ² :1.078	0.583
	Male	%40.0 (n:12)	%28.6 (n:8)		
Hamilton Depression Scale Score	30.3 ± 7.9	28.91 ± 10.0	-	Z: 0.258	0.797
Young Mania Score	3.5 ± 1.0	-	-	-	-
Hospitalization for psychiatric disorder	Median 1 (min 1- max 8)	-	-	-	-
Number of Manic episodes	Median 1 (min 1- max 5)	-	-	-	-
Number of Depressive episodes	Median 2 (min 1- max 6)	Median 2 (min 1- max4)	-	Z:0.953	0.341
Duration of illness (years)	8.2 ± 4.1 (min 1-max 22)	8.04 ± 6.5 (min 2-max 18)	-	Z:0.163	0.871
Age of onset of mental illness	27.1±7.4 (min 17-max 44)	32.4±13.5 (min 17-max 54)	-	Z:1.135	0.176
Abbreviations: BD: bipolar disorder; MDD: major depressive disorder; HC: healthy controls					

There was no difference between the three groups in terms of CRP, HDL, triglyceride, HDL, and irisin. Levels of LDL and total cholesterol in HCs were lower than MDD and bipolar disorder depressive episodes (Table 2).

Table 2. Comparison of blood parameters between Bipolar Disorder Depressive Episode, MDD, and HCs

Study Parameter	Bipolar disorder depressive disorder group (n: 30) (mg/dL)	MDD group (n: 28) (mg/dL)	HC group (n: 30)	Test statistics	p
Insulin	17.98 ± 20.35	14.27 ± 9.50	-	T: 0.395	0.859
C-reactive protein	3.70 ± 4.85	5.23 ± 4.53	1.77 ± 1.22	F: 1.313	0.275
Fasting glucose	91.28 ± 10.26	89.96 ± 11.57	89.52 ± 8.51	F: 0.236	0.790
Triglyceride	8.27 ± 4.12	166.78 ± 82.09	135.04 ± 64.510	F: 1.179	0.313
LDL	117.13 ± 39.69	118.65 ± 39.03	94.46 ± 37.94	F: 3.216	0.045*
HDL	51.50 ± 16.01	55.56 ± 13.42	49.42 ± 11.42	F: 3.011	0.055
Total cholesterol	200.34 ± 46.62	206.41 ± 47.65	169.97 ± 42.52	F: 4.858	0.010**
Irisin	5.60 ± 2.01	4.73 ± 2.56	5.04 ± 2.14	F: 1.139	0.325

Note: *Post-hoc Tukey test revealed statistically difference in LDL levels between BD vs HC, and MDD vs HC ** Post-hoc Tukey test revealed statistical difference in total cholesterol levels between BD vs HC and MDD vs HC. Abbreviations: BD: bipolar depression; MDD: major depressive disorder; HC: healthy controls

In MDD, there was a negative correlation between the duration of illness, the number of depressive episodes, and irisin (Table 3).

Table 3. Comparison of blood parameters between Bipolar Disorder Depressive Episode, MDD, and HCs

Study Parameter	Bipolar Disorder group irisin levels (n: 30)		MDD group irisin levels (n: 28)	
	Spearman rho	p	Spearman rho	p
Duration of illness time	-0.212	0.261	-0.500*	0.007
Manic episode	-0.227	0.228	-	-
Depressive episode	-0.143	0.450	-0.620*	0.001
Hospitalization	-0.258	0.169	-	-
Hamilton Depression Rating Scale Scores	-0.798*	0.001	-0.741*	0.001
Fasting Blood Glucose	0.143	0.458	0.095	0.658
C-reactive protein	-0.013	0.945	0.043	0.392
LDL	0.159	0.400	0.316	0.109
HDL	-0.290	0.120	-0.053	0.794
Total cholesterol	0.093	0.633	0.291	0.141

Note: *. Correlation is significant at the 0.01 level. Abbreviations: BD: bipolar depression; MDD: major depressive disorder; HC: healthy controls

Discussion

There are no therapeutic strategies for BD and MDD, although they are of utmost clinical need. The reason for the lack of therapeutic strategies is that the etiology of bipolar disorder has not been adequately clarified. We evaluated the irisin levels in BD and MDD to help clarify the pathogenesis of these disorders. The effects of irisin on MDD were investigated in an animal study, and it was found that irisin has a role in the induction of antidepressant-like effects in the prefrontal cortex [16]. The low levels of irisin and BDNF in coronary heart disease (CHD)

patients contribute to the occurrence of depression [17]. CHD patients with depression had lower irisin levels compared to CHD patients without depression [18]. The beneficial effects of irisin on mood are related to its inducing effect on the expression of BDNF in the brain [11]. A lot of studies have shown that the level of BDNF in depression is lower than in HCs and that BDNF has a role in antidepressant therapies [18]. The relation between BDNF and irisin suggested that the level of irisin could be affected by depression. Irisin is a crucial regulator of lipid and glucose metabolism and it is necessary for cerebral function [16]. In our study, the levels of LDL and total cholesterol in HCs were lower than in the patient groups. In a study involving patients with obesity, the level of irisin had a positive correlation with levels of total cholesterol and LDL [19]. In another study involving patients with obesity, it was found that the T allele of rs16835198 polymorphism is associated with high total cholesterol and LDL-C and low serum level of irisin [20]. In our study, we did not find any differences between bipolar disorder depressive episodes, MDD and HCs in terms of irisin. These results may be affected by variations in lipid metabolism between patient groups and HCs. Although there were not any differences between all groups (bipolar disorder depressive episode, MDD, and HC) in terms of irisin in our study, a negative correlation was found between BD and MDD regarding HAM-D scores. These results may show that irisin could be affected by the depression in BD and MDD. Similarly, there was also a negative correlation between the number of depressive episodes, duration of disease, and HAM-D scores. The previous metaanalysis showed that the BDNF levels in bipolar depression were lower than healthy controls and there was a negative correlation between BDNF levels and severity of depression in BD [21]. Irisin increases BDNF levels in the brain, and BDNF serves as a transducer, acting as a link between antidepressant drug and the neuroplastic changes that result in the improvement of the depressive symptoms [22]. Over the last decade, several studies have consistently highlighted BDNF as a key player in antidepressant action. An increase in hippocampal and cortical expression of BDNF mRNA parallels the antidepressant-like response of conventional antidepressants such as SSRIs [22]. Considering the fact that irisin is affected by physical activity, the reason for indifferent results between the groups (bipolar disorder depressive episode, MDD, and HC) could be related to having no information about physical activity levels in all groups. The recent study showed that an increase in the level of irisin was found to be positively correlated with increase in the physical activity levels [23]. Another reason could be the use of drugs, as in an animal mania model, using mood stabilizer drugs were found to affect BDNF levels in the rat hippocampus [24]. However, the physical activity may have antidepressant-like effects that could be linked with irisin release and BDNF signaling [25]. The small sample size of the study would also be a limitation.

Conclusion

According to our knowledge, this study is the first to investigate levels of irisin in patients with bipolar disorder depressive

episodes. We found that there were no statistically significant differences between the BD, MDD, and HCs in terms of irisin levels. Future studies involving unmedicated patients could be able to further clarify these results.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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